REMARKS

With reference to the Power of Attorney and Revocation of Prior Powers submitted herewith, Applicants note that new counsel has been appointed to prosecute the present application. As such, Examiner is respectfully requested to direct any and all future correspondence in this matter to Richard H. Zaitlen, Esq. at the address indicated both in the signature block below and in the enclosed Power of Attorney.

Claims 1-20, 25-30 and 36-64 are pending. Claims 21-24 and 31-35 have been cancelled; claims 8 and 36 have been amended; claims 1-20, 25-32 and 36 stand rejected; and claims 37-64 have been added. No new matter has been added. Reexamination and reconsideration of the application, as amended, are respectfully requested.

Claim 8 has been amended to more particularly describe that which Applicants consider to be their invention. Claim 8, as amended, indicates that the embryonic stem cell referred to in claim 7 is *"from the stem cell line murine ES J-1"* (emphasis added). Support for this amendment may be found in the Specification at page 18, lines 27-28.

Claim 36 has been rewritten in independent form to more particularly describe that which Applicants consider to be their invention. Claim 36, as amended, describes *"[a]n animal model for diabetes comprising a null mutant rodent comprising in its germ cells an artificially induced PTTG null mutation."* Support for this amendment may be found in the Specification at page 24, lines 1-12, and in claims 1 and 36 as originally presented.

Newly presented claims 37-41 are substantively similar to cancelled claims 31-35, but have been rewritten in proper process claim format, as is discussed in greater detail in the ensuing remarks. Furthermore, newly presented claims 39-41 are drawn to non-elected subject matter, yet Applicants respectfully submit that these claims must now be taken up for examination pursuant to 37 CFR 1.104, as is appropriate under 35 U.S.C. § 121 (discussed in MPEP 809.04). This is discussed in greater detail in the ensuing remarks.

Newly presented claims 42-64 are substantively similar to pending claims 1-20, 27-30 and 36-41, but are specific to a null mutant *mouse* (claims 42-58), an animal model for the study of diabetes using a null mutant *mouse* (claim 59) and methods of studying mammalian

physiology using a null mutant *mouse* (claims 60-64). Support for these newly presented claims can be found throughout the Specification and in the claims as originally presented.

Examiner objected to claim 36 under 37 CFR 1.75(c), *"as being of improper dependent form for failing to further limit the subject matter of a previous claim,"* and suggested, *inter alia*, that Applicants rewrite the claim in independent form. Claim 36, as amended, is presented in independent form. Thus, Applicants respectfully request withdrawal of this objection.

Examiner rejected claims 31 and 32 under 35 U.S.C. §112, second paragraph, as being indefinite for *"merely recit[ing] a use without any active, positive steps delimiting how this use is actually performed,"* and for Applicants' use of the term "and/or" in these claims, as originally filed. Examiner further rejected claims 31 and 32 under 35 U.S.C. §101 as improper process claims, *"because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process."* Claims 31 and 32 have both been cancelled by virtue of the present Amendment, thus rendering these rejections moot. However, the subject matter of these claims is substantively included in Applicants' new claims 37 and 38, respectively. Applicants were cognizant of Examiner's rejections when drafting these new claims so as to avoid similar issues with respect to 35 U.S.C. §112, second paragraph, and 35 U.S.C. §101.

Moreover, new claims 39-41 are drawn to previously non-elected aspects of Applicants' invention -- they correspond substantively to originally presented claims 33-35, which have been cancelled by virtue of the present Amendment for reasons related solely to format. In the Office Action of January 29, 2003, Examiner restricted the claims of Applicants' invention among five groups. Although Applicant elected Group I (claims 1-20, 25-32 and 36) for further prosecution, Examiner had indicated that Groups I and III (claims 1, 27-31 and 33), IV (claims 1, 27-31 and 34) and V (claims 1, 27-31 and 35) were *linked* by virtue of claims 1 and 27-31. Applicants believe that claims 1, 27-30 and 37 (substantively similar to cancelled claim 31) are now allowable, and therefore respectfully submit that the claims of their invention directed to previously non-elected Groups III, IV and V must be rejoined and fully examined for

patentability under 37 CFR 1.104 (MPEP 809.04).

Examiner rejected claims 1-20, 25-32 and 36 under 35 U.S.C. §112, first paragraph, for a purported lack of enablement. More specifically, Examiner found that *"the specification, while being enabling for the production of a null mutant mouse having null mutation on both pituitary transforming gene (PTTG) alleles in the germ cells and having the phenotypes as disclosed in the specification...does not reasonably provide enablement for production of any null mutant rodent having null mutation on one or both PTTG alleles other than the disclosed null mutant mice."* In light of the teachings of various references, Examiner concluded that *"[i]n view of the inherent unpredictability of the resulting phenotypes of transgenic knockout animals in general and the lack of availability of embryonic stem cells for species other than mouse and rat (no transgenic knockout rat has been successfully produced via homologous recombination of targeting vector in rat ES cells), one skilled in the art at the time of the invention would not know how to make the claimed PTTG null mutant rodents via homologous recombination in ES cells and how to use said PTTG null mutant rodent for the claimed method."* Claims 31 and 32 have been cancelled by virtue of the present amendment, and thus this rejection is rendered moot with respect thereto. With regard to the remaining claims, this rejection is respectfully traversed.

First, Examiner indicated that the Specification fails to provide an enabling disclosure for the preparation of null mutant rodents other than PTTG -/- mice, and the resulting phenotypes of null mutant rodents other than PTTG -/- mice; specifically, *"the phenotypes of heterozygous PTTG +/- null mutant mice."* With respect to these heterozygous PTTG +/- mice, Applicants respectfully draw Examiner's attention to the Specification at page 14, lines 12-20, at page 25, line 1 through page 26, line 21 and Figure 1b, which describe, in detail, the isolation and screening of PTTG +/- mutants (*e.g.*, description of the F_1 generation). Moreover, while it may be true that only phenotypes of homozygous PTTG -/- null mutants are illustrated in the Specification, one of skill in the art would be readily able to detect any number of phenotypes of interest by means well known in the art. Furthermore, any lack of phenotypic description of PTTG +/- null mutants does not negate enablement as to the product claims directed to the mutants themselves. With respect to the claimed method, the Specification having provided the

guidance that the PTTG -/- genotype is associated with diabetes, hyperglycemia, hypoinsulinaemia, hypoleptinemia and a series of other physiological conditions, the skilled artisan would know how to conduct phenotypic screening of PTTG +/- mutants in relation to these conditions, as well. Such screening is performed as a matter of routine in the art, and the application sufficiently describes (and claims) the particular phenotypes for which one would screen these mutant rodents. Therefore, Applicants respectfully submit that the Specification is enabling for homozygous PTTG -/- null mutants *and* heterozygous PTTG +/- null mutants.

Examiner further indicated that the Specification was not enabling for a rodent other than a null mutant mouse, such as a rat, because, allegedly: (1) there is an inherent unpredictability as to the phenotypes of transgenic knockout animals, and (2) no transgenic knockout rat has been successfully produced via homologous recombination of targeting vector in rat ES cells. Applicants address these issues in turn.

1. ***Inherent Unpredictability of Phenotypes of Transgenic Knockout Animals***

Examiner cited Wu *et al.* (*Methods in Gene Biotechnology*, CRC Press, Boca Raton, p. 339-365 [1997]; "Wu") to support the assertion that phenotypic results are unpredictable such that knockout mutations can sometimes result in early death of embryos or young animals, or can cause other abnormalities. Examiner further cited Sigmund (*Arterioscler. Thromb. Vasc. Biol.*, p.1425-1429 [June 2000]) and Wolfer *et al.* (*Trends in Neurosciences*, 25(7):336-340 [2002]; "Wolfer") for the proposition that variation in their genetic background makes the resulting phenotypes of transgenic animals unpredictable. For example, Examiner noted that the abstract of Sigmund states that *"animals containing the same exact genetic manipulation exhibit profoundly different phenotypes when present on diverse genetic backgrounds,"* and that Wolfer indicates that flanking-gene or linkage disequilibria can contribute to such phenotypic differences.

A claim is enabled so long as an individual of reasonable skill in the art *"could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation."* United States v. Telectronics, Inc., 857 F.2d 778, 785 (Fed. Cir. 1988); MPEP § 2164.01. Furthermore, *"[a]s long as the Specification discloses at least one*

method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 U.S.C. 112 is satisfied" (emphasis added). In re Fisher, 427 F.2d 833, 839 (CCPA 1970); MPEP § 2164.01(b). Moreover, Examiner emphasizes the unpredictable nature of certain aspects of this field of art in concluding that "undue experimentation" would be required to practice the methods of Applicants' invention. True, experimentation would be required to practice these methods, and the amount of that experimentation may even be substantial in some instances, but experimentation is permissible and is not a bar to enablement. Even *"a considerable amount of experimentation is permissible, if it is merely routine."* In re Wands, 858 F.2d 731, 737 (Fed. Cir. 1988); MPEP § 2164.01. In Telectronics, for example, competitors had to experiment for 6 to 12 months, call upon four different specialists (an electrical engineer, a surgeon, a biomechanic, and a biologist), and spend $50,000 to determine how to practice the invention at issue; yet even this amount of experimentation was not undue, because the steps required to carry it out were routine.

In the instant case, Applicants' Specification includes detailed instructions and examples that would allow one of skill in the art to practice the invention without undue experimentation. The Specification describes methods for creating a PTTG null mutant, and further indicates that the screening of progeny may be implemented to identify transgenic animals (page 22, lines 9-10). With respect to Examiner's reference to the unpredictability of mutant phenotypes, phenotypic screening, such as that noted above, may be readily implemented by one of skill in the art by methods known at the time of the invention to identify mutant rodents that possess a desired trait and that do not possess others. Such methods can be used to avoid, by way of example, the undesirable phenotypes noted by the Examiner from the Wu reference (*i.e.*, early death of embryos or young animals). Concededly, this may involve considerable expense in some instances, and there may be situations where the methods employed in connection with the invention do not result in a successful gene transfer procedure with respect to each and every animal subjected to the procedure. This is precisely the issue described in the Wolfer reference, which Examiner relies upon for the proposition that flanking-gene or linkage disequilibria can contribute to phenotypic differences. But the Wolfer reference repeatedly points out that there

are numerous, known methods by which to screen for these problems -- the limitation of those methods is simply that they are too costly. Wolfer additionally recognizes that *"the statistically expected number of confounding flanking genes is relatively low."* In sum, there are methods that may be readily employed to address the issues discussed in Wolfer, they are simply not used on a regular basis because they are expensive, and the problems they address arise only infrequently.

Considerable expense and the need for testing does not equate to a lack of enablement. Moreover, the occasional unsuccessful gene transfer procedure is to be expected, as is well known to the skilled artisan. By way of example, Asamoto *et al.* (*Carcinogenesis*, 21(2):243-49 [2000]; "Asamoto"; EXHIBIT A) describes the preparation of transgenic rats carrying human c-Ha-*ras* proto-oncogenes by microinjection of a *Bam*HI fragment of the human oncogene with its own promoter region into pronuclei of rat embryos. In Asamoto, 1145 rat embryos collected from superovulated prepubescent Sprague-Dawley female rats were microinjected, resulting in 211 potential transgenic rats prepared by techniques "similar to those commonly used for transgenic mice." Screening by PCR and Southern blotting identified only two male rats that carried the transgene.

This is a tremendously complex field of art, and a significant amount of testing and experimentation is required to develop and screen nearly any transgenic animal. However, this does not imply that the claimed methods are insufficiently enabled. In fact, this issue has been revisited on numerous occasions by the courts, and every time the answer is the same -- that the need for substantial but routine experimentation does not preclude patentability on grounds of enablement, and this doctrine applies equally to the patentability of transgenic animals. *Elan Pharm., Inc. v. Mayo Found. for Med. Educ. and Res.*, No. 00-1467 (Fed.Cir. reversed and remanded for factual determination regarding enablement Oct. 2, 2003). Thus, Applicants respectfully submit that any perceived unpredictability of their methods may be adequately accounted for with conventional phenotypic screening procedures, and that a need to employ such procedures does not negate the enablement of their claims.

2. ***Production of Transgenic Knockout Rat via Homologous Recombination of Targeting Vector in Rat ES Cells***

Examiner cited Houdebine (*J. Biotechnol.*, 34:269-87 [1994]) and Seamark (*Reprod. Fertil. Dev.*, 6:653-657 [1994]) for the propositions that, respectively, ES cells are only available in mice, and that the totipotency of transfected ES cells is unpredictable. Applicants respectfully point out that these references predate the invention by seven years, and thus do not accurately reflect the state of this art as of the date of the invention. In fact, Examiner hastened to point out that, at the time of the invention, rat ES cells were already known in the art. This is not apparent from Houdebine, as this reference is simply too old to be relied upon as a proper indication of the overall state of the art at the time of the invention.

Notwithstanding the age of these references, Examiner appears to ignore the fact that while Houdebine and Seamark both seemingly predate the isolation and use of ES cells from rodents other than mice, both of these references state that male and female germ cells, rather than ES cells, can be used to generate chimeric animals. In fact, the references provide examples of a host of transgenic animals created in this manner (*See* Houdebine, Table 6 and Seamark, p. 653-657). These alternate procedures are described throughout Applicants' Specification and claims. More particularly, the Specification teaches that methods other than homologous recombination in ES cells can be used in accordance with various embodiments of the invention. And, as noted above, to satisfy the enablement requirement of 35 U.S.C. §112, the Specification need only disclose *"at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim."* Fisher, 427 F.2d at 839. In this regard, Applicants describe (and claim) the use of transpositional recombination, site-directed mutagenesis and frame shift mutation both in ES cells and in oocytes and male germ cells at page 13, line 21 through page 14 line 11 of the Specification, and in the claims; for example, claims 15-20, which have remained unchanged since originally presented, and claims 53 and 54, which have been added by virtue of the present amendment. These methods are known in the art and can be implemented without undue experimentation.

A multitude of transgenic rat models have been developed and used in the research context; most of these models employ microinjection techniques to introduce the transgene.

These methods are well known and commonly used in the art, and may be employed in connection with various aspects of the present invention without undue experimentation. By way of example, Asamoto describes a transgenic rat carrying human c-Ha-*ras* proto-oncogenes, generated with microinjection techniques. Additionally, Thorsell *et al.* (*Proc. Natl. Acad. Sci. USA*, 97(23):12852-857 [2000]; EXHIBIT B) describe the preparation of transgenic rats that overexpress neuropeptide Y; Smith *et al.* (*Molecular and Cellular Biol.*, 21(11):3704-13 [2001]; EXHIBIT C) describe the preparation of transgenic rats in which a dominant negative version of Fos-related antigen 2 (Fra-2) is expressed in the pineal gland; and Reid *et al.* (*Proc. Natl. Acad. Sci. USA*, 98(16):9271-76 [2001]; EXHIBIT D) describe the preparation of the first HIV-1 transgenic rat. In fact, transgenic rats are commercially available -- Big Blue® rats, available from Stratagene (La Jolla, CA), are routinely used for and were developed for the purpose of detecting mutant frequency and mutant spectra. For instance, in Sato *et al.* (*Carcinogenesis*, 21(4):653-61 [2000]; EXHIBIT E), Big Blue® rats were used to study the mutant frequency in lung tissue of animals exposed to increased levels of diesel exhaust. Other studies describe the use of still further methods of generating transgenic animals. For example, Hayes *et al.* (*Physiol. Genomics*, 5:193-203 [2001]; EXHIBIT F) report the successful generation of transgenic rats in several studies by nuclear transfer.

There are a host of methods that may be employed in connection with various embodiments of the present invention to generate mutant animals. These methods are not limited to mice, but, instead, may be used to prepare transgenic mice, rats and still further animals. Similar techniques are widely and routinely used in the art, as is illustrated by the various references cited herein.

In sum, the threshold for enablement is not quite as high as Examiner suggests. Applicants need only describe their invention such that one of skill in the art could practice their invention without undue experimentation. Moreover, the disclosure of one method that bears a reasonable correlation to the claimed invention suffices for enablement. There are a number of methods known in the art at the time of the invention that may be employed to generate the Applicants' mutant animals. Homologous recombination of a targeting vector in ES cells is one

such method, yet a number of alternative methods both described in the Specification and known in the art may be employed.

It is respectfully submitted that Applicants' Specification, in light of the common knowledge in the art at the time of the invention, is sufficient to enable the claims as currently presented. Applicants thus respectfully submit that claims 1-20, 25-30 and 36 are adequately enabled by the Specification and therefore respectfully request withdrawal of this rejection under 35 U.S.C. §112, first paragraph.

Applicants believe that the foregoing amendments place the application in condition for allowance, and a favorable action is respectfully requested. If for any reason Examiner finds the application other than in condition for allowance, the Examiner is requested to call the undersigned attorney at the Los Angeles telephone number (213) 488-7100 to discuss the steps necessary for placing the application in condition for allowance should Examiner believe that such a telephone conference would advance prosecution of the application.

Respectfully submitted,
PILLSBURY WINTHROP LLP

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By: _____
Seth D. Levy
Registration No. 44,869
Attorney for Applicant(s)

725 South Figueroa Street, Suite 2800
Los Angeles, CA 90017
Telephone: (213) 488-7100
Facsimile: (213) 629-1033

Enclosure: Power of Attorney from Assignee and Revocation of Prior Powers
Petition for Three Month Extension of Time